be helped by the introduction of high-throughput multiplex genotyping, which will enable simultaneous sequencing and measuring copy numbers of hundreds of genes from only nanograms of cancer cell DNA.

Although these advances will probably reduce the proportion of patients who need chemotherapy, it will remain the main treatment option for advanced NSCLC. The TAILOR study will contribute to more rational use of chemotherapy and EGFR tyrosine kinase inhibitors in the treatment of NSCLC, based on its molecular profile.

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Combination endocrine treatments unproven in breast cancer

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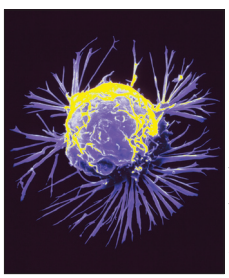
Ovarian ablation, which was introduced more than 100 years ago, was the first endocrine treatment for advanced breast cancer, followed by adrenalectomy and hypophysectomy. These ablative therapies have since been replaced by antioestrogen treatments, luteinising-hormone-releasing hormone agonists, and aromatase inhibitors.[1] Other endocrine treatments with different mechanisms of action have also become available for breast cancer: oestrogens, progestins, androgens, antiandrogens, and selective oestrogen-receptor downregulators.

Although the superiority of combinations of chemotherapeutic agents with different mechanisms of action to single agents has been established in the treatment of early and advanced breast cancer,[2] that of combinations of endocrine treatments has not been shown.[1] Several combinations of hormonal agents have been assessed in patients with advanced breast cancer, with no consistent improvement in either time to progression of disease or survival.[3] Additionally, the combination of an antioestrogen treatment (tamoxifen) and ovarian suppression with a luteinising-hormone-releasing hormone agonist does not lead to improvements in disease-free or overall survival when compared with antioestrogen treatment alone in premenopausal women with early breast cancer.[4] A large, prospective, double-blind trial[5] comparing tamoxifen with an aromatase inhibitor (anastrozole) and tamoxifen or anastrozole alone as adjuvant treatment for breast cancer showed that the combination did not improve either disease-free or overall survival. Indeed, the group who received the combination was discontinued after initial analysis of the data.[5]

Because preclinical data[6] suggested that the combination of an aromatase inhibitor and fulvestrant—a member of the newest class of hormonal agents, selective oestrogen receptor downregulators—was superior to either agent alone against breast tumours in mice, three prospective studies[7–9] have assessed this approach in postmenopausal women with advanced breast cancer. In *The Lancet Oncology*, Stephen Johnston and colleagues report results of a phase 3, European, multicentre trial.[7] Postmenopausal women with hormone-receptor-positive breast cancer who had relapsed or progressed while receiving a non-steroidal aromatase inhibitor were randomly assigned to receive fulvestrant plus anastrozole, fulvestrant plus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anastrozole-matched placebo, or the steroidal aromatase inhibitor exemestane. No improvement in progression-free survival was recorded in the group who received fulvestrant plus anastrozole (median 4·4 months, 95% CI 3·4–5·4) compared with fulvestrant plus placebo (4·8 months, 3·6–5·5; hazard ratio [HR] 1·00, 95% CI 0·83–1·21; log-rank p=0·98), or in the group given fulvestrant plus placebo compared with exemestane (3·4 months, 3·0–4·6; HR 0·95, 0·79–1·14; log-rank p=0·56).

Another phase 3 study[8] comparing the combination of anastrozole and fulvestrant as first-line treatment in postmenopausal patients with hormone-receptor-positive advanced breast cancer also showed no advantages in terms of clinical efficacy for the combination compared with anastrozole alone. By contrast, a phase 3 trial from North America[9] compared the combination of anastrozole and fulvestrant with anastrozole alone as first-line treatment in postmenopausal women with hormone-receptor-positive advanced breast cancer, and showed increased control of disease and survival with the combination of fulvestrant and anastrozole. However, the apparent improvements could have been due to imbalances in prognostic characteristics between the two study groups.

Therefore, there are still no consistent data to support the notion that combination endocrine therapy is superior to treatment with one agent in early or advanced breast cancer. However, as understanding of the mechanisms of resistance to endocrine treatment has improved, targeting of some pathways has resulted in new approaches that offer hope for disease control. For example, postmenopausal patients with hormone-receptor-positive, HER2-positive advanced breast cancer given endocrine and anti-HER2 treatments have had longer control of disease than have those given endocrine treatment alone.[1] Indeed, a combination of an aromatase inhibitor with an anti-HER2 treatment has been approved by the US Food and Drug Administration for the management of postmenopausal patients with hormone-receptor-positive, HER2-positive advanced breast cancer.[1] Another effective approach has been the combination of an mTOR inhibitor (everolimus) with exemestane.[10] The combination of exemestane with a histone deacetylase inhibitor (entinostat) has also had encouraging results.[11]

In conclusion, a combination of endocrine agents with different mechanisms of action will probably not result in a meaningful improvement in outcomes for patients with breast cancer. Sequential use of endocrine agents remains the standard of care in patients with advanced breast cancer. However, understanding of the mechanisms of resistance to hormonal agents continues to advance, and combinations of endocrine treatment with targeted agents that block resistance pathways should improve the outlook for patients with breast cancer that is resistant to endocrine treatment.

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